PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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Dr. William Stokes
Director, NICEATM
National Institute of Environmental Health Sciences
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Via electronic transmission to: iccvam@niehs.nih.gov

Dear Dr. Stokes:

These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) and our more than 750,000 members and supporters in response to a July 1 notice in the *Federal Register* inviting public comment on three sets of "Minimum Performance Standards" for *in vitro* skin corrosivity tests proposed by the Dermal Corrosivity and Irritation Working Group of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). We appreciate the work that has gone into the development of these documents and are hopeful that they will not only satisfy the needs of U.S. regulatory agencies, given their inability to lawfully require or recommend use of proprietary test methods, but will also be useful in preventing future bottlenecks in the validation pipeline both domestically and internationally.

PETA is in general agreement with the content of ICCVAM's proposed Minimum Performance Standards, with one notable exception: we strongly disagree with ICCVAM's recommendation that fully-validated *in vitro* human skin model systems (i.e., EpiDerm™ and EPISKIN™) be relegated to the status of merely "positive screens," whereby "substances that are negative *in vitro* might undergo additional testing in accordance with the tiered testing strategy" (*In Vitro* Human Skin Model MPS, p. 3), or, as articulated in ICCVAM's official recommendations to federal agencies: "Negative *in vitro* corrosivity responses shall be followed by *in vivo* dermal corrosion/irritation testing" (66 *Fed. Reg.* 49685).

As you know, both the European Union and the 30-member-country Organization for Economic Cooperation and Development (OECD) have accepted these validated *in vitro* human skin model systems either as stand-alone methods or as part of a purely *non-animal* weight-of-evidence strategy. Given ICCVAM's statutory mandate to promote the replacement, reduction, or refinement of animal-based testing and to strive for the elimination of unnecessary and duplicative efforts (42 *U.S.C.* Sec. 2851-3(b)), we cannot comprehend why ICCVAM persists in advocating a testing paradigm that is so clearly out-of-step with the international consensus on this issue.

It is also worth reiterating a point that was raised several times during the August 12-13 meeting of the National Toxicology Program's Scientific Advisory Committee on Alternative Toxicological Methods: that only a miniscule number (estimates range from two to six percent) of chemicals in commerce today are believed to possess irritating or corrosive properties. Thus, if regulatory agencies adhere to ICCVAM's testing recommendations (i.e., 66 *Fed. Reg.* 49685) and accept *in vitro* skin corrosivity assays as merely "positive screens," only a tiny handful of chemicals would likely be classified on the basis of *in vitro* data, while the overwhelming majority would still be required to undergo animal testing, ostensibly to "confirm" *in vitro* findings of non-corrosivity. From this perspective, ICCVAM's testing recommendations not only squander a golden opportunity for replacement, they promise to be equally meaningless and ineffectual from a reduction standpoint as well.

Even recognizing ICCVAM's stated concern regarding the potential for "false-negative" results *in vitro*, we should not need to remind the committee or its member agencies that the animal-based

reference data against which *in vitro* assays are so often compared have themselves seldom, if ever, been formally validated to demonstrate either their intra- or inter-laboratory reproducibility, much less their relevance to human beings. As just one example, we call your attention to a comparison of data from skin irritation tests on rabbits and skin patch tests on human volunteers for 65 substances, which found that nearly half—fully 45 percent—of classifications of chemical irritation potential based on animal tests were incorrect (MK Robinson et al. *Food Chem Toxicol* 40, 573-592, 2002).

As we have also pointed out in previous correspondence, a 1998 study by Worth and colleagues (*ATLA* 26, 709-720) determined that "false-negative" results from human skin equivalent models ***can be reduced to zero*** when combined with pH measurements and computerized structure-activity relationship modeling. The fact that this study is based on modeling data as opposed to a multi-chemical, multi-laboratory validation exercise should not, in itself, be seen to diminish the significance of the study's findings. Indeed, ICCVAM has already established a precedent for the acceptance of modeling data for validation purposes through its endorsement of the revised Up-and-Down Procedure for acute toxicity, the "validation" of which was based *entirely* on computer modeling.

Nonetheless, if ICCVAM and/or its constituent agencies had lingering doubts regarding the findings of Worth *et al.* (1998), they have had ample opportunity in the more than four years since this study was published to either confirm or refute its assertions. However, to the best of our knowledge, no such study has been undertaken by any ICCVAM member agency, which calls into question ICCVAM's continued resistance to a non-animal weight-of-evidence approach and its inexplicable insistence on "confirmatory" testing *in vivo*. Clearly, the former scenario is not only more humane, but also fully in harmony with the international consensus on this issue—both considerations being directly relevant to ICCVAM's statutory mandate.

With these considerations in mind, we strongly urge ICCVAM to revise its proposed Minimum Performance Standards and testing recommendations for *in vitro* human skin corrosivity systems to bring them into line with international regulations (e.g., EU Annex V) and testing guidelines (e.g., OECD 431).

Thank you for your attention and responsiveness to these comments.

Sincerely,

/s/

Troy Seidle
Science Policy Advisor